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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/543,122	04/20/2006	Sudha Shenoy	067437-5020US	2631

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EXAMINER	
HOWARD, ZACHARY C	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/543,122	**Applicant(s)** SHENOY ET AL.	
	Examiner ZACHARY C. HOWARD	**Art Unit** 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 January 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,2,4-7,18 and 20-22*.
   Claim(s) withdrawn from consideration: *8-18 and 23-35*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Bridget E Bunner/
Primary Examiner, Art Unit 1647

It is noted that the claims filed on 1/28/09 appear to be a courtesy copy of the claims because no amendments have been made with respect to previous listing of the claims (filed on 7/28/08).

Continuation of 11. does NOT place the application in condition for allowance because:

Claims 1, 2, 4-7, 18 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an arrestin chimera comprising a naturally occurring beta-arrestin-2 and a naturally occurring ubiquitin moiety (including an arrestin chimera comprising SEQ ID NO: 2), wherein the arrestin chimera has an increased affinity for a GPCR, as compared to the affinity of a wild-type arrestin, and wherein increased affinity means that the arrestin chimera remains associated with the GPCR and traffics with the GPCR into endosomes, and wherein the arrestin chimera does not dissociate at or near the plasma membrane, does not reasonably provide enablement for an arrestin chimera comprising an arrestin or a fragment of arrestin and a ubiquitin moiety or a fragment of ubiquitin, wherein the arrestin chimera has an increased affinity for a GPCR, as compared to the affinity of a wild-type arrestin, and wherein increased affinity means that the arrestin chimera remains associated with the GPCR and traffics with the GPCR into endosomes, and wherein the arrestin chimera does not dissociate at or near the plasma membrane. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection was set forth previously and maintained at pg 3-10 of the 10/28/08 Office Action.

Applicants' arguments (1/28/09; pg 6-10) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response at pg 6-7, Applicants characterize the test for enablement, citing United States v Telectronics Inc (1989), MPEP 2164.01, the Wands factors, and Amgen, Inc. v. Chugai Pharm Co.

Applicants' characterization of the test for enablement has been fully considered and is not disputed. However, it is maintained that the rejection set forth previously met the standards for an enablement rejection in accordance with each citation.

In the response at pg 7-10, Applicants argue that because the specification enables an arrestin chimera comprising a naturally occurring beta-arrestin-2 and a naturally occurring ubiquitin moiety, then variations of such a chimera are also enabled by the disclosure coupled with the teaching of the art. Applicants argue that the skilled artisan could use "standard methods known in the art to extrapolate from the assays described in the present specification to determine whether an arrestin chimera is within the scope of the present claims" (pg 7). Throughout the response, Applicants argue that the unpredictability of whether a particular chimera has increased affinity for GPCR is balanced by the ease and routine nature of assays to detect that a transfer has taken place. Applicants point to assays described at pages 29-34 (including paragraphs [0123-0127]), pages 38-43, 43-49 (including paragraphs [0185]-[0192]), pages 51-60 (including the Examples on pages 54-56 and in paragraphs [0210] and [0241]). Applicants further argue that test for enablement is not whether a skilled artisan could predict whether a particular chimera would have functionality, but whether determining this functionality requires undue experimentation. Applicants further argue that complex experimentation is not necessarily undue, citing MPEP 2164.01 and "the Wands court" (pg 8), and that "practitioners in the art of molecular biology frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation" (pg 8). Applicants argue that "Federal Circuit has found such experimentation is not undue" but without any citation in support. Applicants further argue that "even if a large number of variants are encompassed by the present claims, the number of possible variants alone can not be used to support a rejection for enablement" (pg 9). Applicants further argue that compliance with the enablement requirement does not require a working example.

Applicants' arguments have been fully considered but are not found to be persuasive.

The instant rejection is not based solely on the number of possible variants encompassed by the claims. Furthermore, the instant rejection is not based solely whether a skilled artisan could predict which variants are functional. Furthermore, the instant rejection is not based solely on the limited working examples in the specification. Instead, the rejection set forth previously and maintained herein is based on a proper Wands analysis that included the 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention, as factors that were considreed in said analysis, and which concluded that undue experimentation was required to practice the full scope of the claimed invention.

The Examiner does not dispute that the specification teaches assays for determining whether a particular chimera containing a variant of arrestin and/or ubiquitin has the functional activity recited in the claims ("an increased affinity for a GPCR, as compared to the affinity of a wild-type arrestin for a GPCR, and wherein increased affinity means that the arrestin chimera remains associated with the GPCR and traffics with the GPCR into endosomes, and wherein the arrestin chimera does not dissociate from the GPCR at or near the plasma membrane"). The specification describes testing of one particular arrestin chimera (SEQ ID NO: 2) in such assays, and as such provides enablement for such a chimera, as indicated in the rejection set forth previously.

However, the rejection is maintained because the claims encompass an essentially unlimited genus of chimeras of arrestin and ubiquitin variants, and the absence on any guidance in the specification as to which variants are functional, the skilled artisan would need to make and test a representative number of said genus in order to determine whether or not they meet the functional limitations recited in the claims, and this would require undue experimentation. As set forth previously, the sequence of the fusion protein of SEQ ID NO: 2 consists of 525 amino acids, of which presumably ~238 correspond to the YFP (yellow fluorescent protein), indicating that ~287 correspond to the β-arrestin2 and ubiquitin proteins. As ubiquitin consists of 76 amino acids, the β-arrestin2 is ~211 amino acids. Thus, engineered variants of β-arrestin2 and ubiquitin together include up to ~287 different amino acid sites that can be altered by mutation (substitution, deletion or

addition). The claims place no limitation on the number of mutations that can be included in the claimed chimeric protein. The art of record teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, and that function cannot be predicted from structure alone. The essentially limitless size of the genus to be tested (no structural limitations are required by the claims) coupled with the lack of guidance (in the specification) and the lack predictability (as taught by the relevant art cited in the rejection) in which mutations in the arrestin and/or ubiquitin will impact the functionality of chimera, renders the experimentation undue.

Assuming for the sake of argument that the genus of variants was limited to those that are at least 90% identical to the amino acid sequence of the β-arrestin2 and ubiquitin portions (238 amino acids) of SEQ ID NO: 2 (525 amino acids). Such variants would include those with up to 23 changes (i.e., 10% of 238).

To put this situation in perspective, the number of possible amino acid sequences that are 100 amino acids in length is 20^{100} (~10^{130}). The number of possible amino acid sequences that are of a given % identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X2L(L-1)/2! + X3L(L-1)(L-2)/3! + ... + Xn-1L(L-1)(L-2)...(L-(n-2))/(n-1)! + XnL(L-1)(L-2)...(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence (X = 19 for a polypeptide sequence), L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For example, for a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6 x 10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1 x 10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula XnLn/n!, where n<<L. Using this formula to approximate N in this example gives a value of 1.7 x 10^{26} .

Applying this to the instant claims, the reference amino acid sequence is 232 amino acids long. A sequence that is at least 90% identical tolerates up to 23 amino acid changes. Therefore, the total number of possible amino acid sequences that are at least 90% identical is about 2.5 x 10^{61} (19^{23} * 232^{23}/23!). This value is more than a billion billions and approaches the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, while limiting the scope of potential sequences to those that are at least 90% identical to a reference greatly reduces the number of potential sequences to test (as compared to having no structural limitation at all as in the instant claims), it does not do so in any meaningful way. Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those which encode a protein having the recited functional limitation. Such a genus is so vast that it would clearly require undue experimentation for the skilled artisan to make and test even a representative number of species from the genus. The representative species would need to range across the full scope of the claims, because each mutation increases the chance of impacting the functionality of the protein.

Furthermore, the instant claims are not even limited to variants that are at least 90% identical to the portion of SEQ ID NO: 2 comprising arrestin and ubiquitin. Instead, the claims encompass an essentially unlimited number of variants.

Thus, it is maintained that due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.